INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2009/043644

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl.

C07D 491/044 (2006.01) *A61K 31/655* (2006.01) *A61P 31/04* (2006.01)
A61K 31/407 (2006.01) *A61P 29/00* (2006.01) *A61P 35/00* (2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Registry, CAplus: substructure search based on Formula (I) of claim 1

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2007/130404 A1 (NEREUS PHARMACETUICALS, INC.) 15 November 2007 See abstract; formula II-22 and II-41; pp37, 45, 114, 118, 138, 158, 159, 169 & 182-184; para [0010], claim 2	1-46, 129, 134-138
Y	MACHERLA et al. "Structure-Activity Relationship Studies of Salinosporamide A (NPI-0052), a Novel Marine Derived Proteasome Inhibitor" *J. Med. Chem.*, **2005**, 48(11), 3684-3687 See abstract, p3687	1-46, 129, 134-138

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
18 September 2009

Date of mailing of the international search report
28 SEP 2009

Name and mailing address of the ISA/AU

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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	TAKASHI et al. "Silver Fluoride Supported on Calcium Fluoride. Improved Fluorination and Halofluorination Reactions" *Chemistry Letters* **1988**, (11), 1877-1878 See whole document.	
P,X	MANAM et al. "Leaving Groups Prolong the Duration of 20S Proteasome Inhibition and Enhance the Potency of Salinosporamides" *J. Med. Chem.*, **2008**, 51(21), 6711–6724; published 22 October 2008 See abstract; compound 19; Scheme 3; "Concluding remarks".	1-4, 17-20, 22, 23, 128, 129, 134-138

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report	Patent Family Member
WO 2007/130404	NONE

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

END OF ANNEX

From the:
INTERNATIONAL SEARCHING AUTHORITY

To:

Knobbe Martens Olson & Bear LLP
2040 Main Street
14th Floor
Irvine, California 92614
United States of America

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	28 SEP 2009
Applicant's or agent's file reference NEREUS.183VP	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2009/043644	12 May 2009	12 May 2008

International Patent Classification (IPC) or both national classification and IPC
Int. Cl.

C07D 491/044 (2006.01) ***A61K 31/655*** (2006.01) ***A61P 31/04*** (2006.01)
A61K 31/407 (2006.01) ***A61P 29/00*** (2006.01) ***A61P 35/00*** (2006.01)

Applicant

NEREUS PHARMACEUTICALS, INC.

1. This opinion contains indications relating to the following items:

[X]	Box No. I	Basis of the opinion
[X]	Box No. II	Priority
[ ]	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
[ ]	Box No. IV	Lack of unity of invention
[X]	Box No. V	Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
[ ]	Box No. VI	Certain documents cited
[ ]	Box No. VII	Certain defects in the international application
[ ]	Box No. VIII	Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA	Date of completion of this opinion	Authorized Officer
AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. +61 2 6283 7999	18 September 2009	**ALICA DALY** AUSTRALIAN PATENT OFFICE (ISO 9001 Quality Certified Service) Telephone No. +61 3 9935 9606

Box No. I Basis of this opinion

1. With regard to the **language,** this opinion has been established on the basis of:

   [X] The international application in the language in which it was filed

   [ ] A translation of the international application into, , which is the language of a translation furnished for the purposes of international search (under Rules 12.3(a) and 23.1(b)).

2. [ ] This opinion has been established taking into account **the rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:

   a. (means)

      [ ] on paper

      [ ] in electronic form

   b. (time)

      [ ] in the international application as filed

      [ ] together with the international application in electronic form

      [ ] subsequently to this Authority for the purposes of search

4. [ ] In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

International application No.
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Box No. II Priority

1. ☐ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

The priority document contains a valid disclosure of the invention which is the subject of the current application *in so far as* it relates to the subject matter that is disclosed in the prior published document, D4.

Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	**1-138**	**YES**
	Claims	**NONE**	**NO**
Inventive step (IS)	Claims	**47-128, 130-133**	**YES**
	Claims	**1-46, 129, 134-138**	**NO**
Industrial applicability (IA)	Claims	**1-138**	**YES**
	Claims	**NONE**	**NO**

2. Citations and explanations:

The following documents identified in the International Search Report have been considered for the purposes of this report. Full bibliographic details are provided in the International Search Report:

D1 WO 2007/130404
D2 Macherla et al. *J. Med. Chem.* **2005**, 48(11), 3684-3687
D3 Takashi et al. *Chemistry Letters* **1988**, (11), 1877-1878
D4 Manam et al. *J. Med. Chem.* **2008**, 51(21), 6711–6724

The present claims define Salinosporamide derivatives of formula (I) that include a sulfonate ester, ester or ether group in the substituent at the 4-position of the 6-oxa-2-azabicyclo[3.2.0]heptane-3,7-dione moiety. These derivatives can be included in pharmaceutical compositions and can be used as proteasome inhibitors for treating or ameliorating a disease or condition such as cancer, a microbial disease or inflammation.

Non-patent Literature P Category Documents

With regard to D4, this non-patent literature document discloses subject matter that is of particular relevance to this application. However, it was published after the priority date of the current application and under the PCT, only documents published before the priority date of the application being considered deprive the claims of that application of novelty. As the current application has a valid priority claim with regard to the subject matter disclosed in D4, it is not considered to be relevant in this opinion.

NOVELTY (N)

D1 discloses Salinosporamide analogues and methods of using them for the treatment of lung cancer (abstract). D1 discloses an ethyl ester derivative (formula II-22, pp37 & 114) and a mesylate derivative (Formula II-41, pp45 & 118) of Salinosporamide A, which would be novelty destroying for the current claims except that the molecular weight of said substituents does not meet the proviso of claim 1. Therefore D1 is not relevant for novelty.

D2 discloses structure-activity relationships (SAR) of Salinosporamide derivatives (abstract). D2 does not disclose any compounds with a sulfonate ester, ester or ether group with the 4-position of the 6-oxa-2-azabicyclo[3.2.0]heptane-3,7-dione moiety. Therefore D2 is not relevant for novelty.

D3 discloses fluorination reactions using silver fluoride supported on calcium fluoride. D3 is not relevant for novelty.

None of the citations disclose a compounds of Formula (I) of the current claims with a sulfonate ester, ester or ether group on the side chain that has a molecular weight over 92 $gmol^{-1}$ for the sulfonate or 77 $gmol^{-1}$ for the ester or ether; or a method for synthesising a compound of formula (B) using a silver reagent. Therefore the subject matter of claims 1 and 128 and their dependent claims is new and meets the requirements of Article 33(2) of the PCT with regard to novelty.

[continued in Supplemental Box]

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**

Continuation of: **Box V**

INVENTIVE STEP (IS)

Claims 1-127 and 129-138: D1 is considered to be the closest prior art. D1 discloses heterobicyclic γ-lactam-β-lactone derivatives of formula II (claim 2) as proteasome inhibitors (para [0010]). The general structure of formula II of D1 encompasses the compounds of the current application wherein R_1 is substituted alkyl. The difference between the exemplified compounds of D1 and the current compounds is that compounds II-22 and II-41 of D1 do not satisfy the molecular weight proviso defined in claim 1 of the current application. Both D1 and D2 disclose that derivatives of Salinosporamide A with a haloethyl sidechain at the 4-position of the bicycle are the most potent proteasome inhibitors (D1, p182-184; D2, abstract). D1 suggests that this is due to halo groups being good leaving groups and suggests that compounds with good leaving groups promotes the delivery of the compound to its target, thereby enhancing its therapeutic effect (p182-184). Furthermore, D2 suggests that the role of the halo group *in vivo* is mechanistic, and also acts a leaving group, and that analogues with alternative functional groups at the 4-position be prepared (p3687).

The problem to be solved by the current application in light of the prior art is the provision of further proteasome inhibitors derived from Salinosporamide A. The difference between D1 and the current application resides in what is merely a choice of one of several obvious known alternatives which would be available for use by the person skilled in the art. It is considered that a skilled person, when faced with the problem of providing further compounds with proteasome inhibitory activity, would prepare further derivatives with good leaving groups, as suggested by D2. It is well known in the art that sulfonate derivatives a good leaving groups. The specification describes no particular problem to be overcome which would act as a barrier in applying such a known alternative without an inventive solution, nor is such a solution described. The exemplified sulfonates of the current application have a similar inhibitory profile to the known sulfonates with smaller leaving groups. Therefore this is merely an obvious choice which the person skilled in the art would arrive at by a routine and non-inventive process. Therefore the subject matter of claims 1-46, 129 and 134-138 is obvious and does not meet the requirements of Article 33(3) of the PCT with regard to inventive step.

With regard to the ether and ester derivatives, the prior art teaches against these derivatives as the prior art suggests that a leaving group is required for the activity, as the ethyl ester derivative II-22 of D1 has very poor activity compared with the halo derivatives (pp138, 158, 159 & 169). Therefore the subject matter claims 47-127 and 130-133 is not obvious as they relate to non-leaving group derivatives and meets the requirements of Article 33(3) of the PCT with regard to inventive step.

Claim 128: The subject matter of claim 128 is not obvious as the silver reagents defined in the claim are not known to produce hydroxy compounds (see D3) and meets the requirements of Article 33(3) of the PCT with regard to inventive step.

INDUSTRIAL APPLICABILITY (IA)

The invention defined in the claims is considered to meet the requirements of Industrial Applicability under Article 33(4) of the PCT because it can be made by, or used in, industry.

PATENT COOPERATION TREA

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference NEREUS.183VP	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. **PCT/US2009/043644**	International filing date *(day/month/year)* 12 May 2009	(Earliest) Priority Date *(day/month/year)* 12 May 2008

Applicant

NEREUS PHARMACEUTICALS, INC.

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 5 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language,** the international search was carried out on the basis of:

☒ The international application in the language in which it was filed.

☐ A translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).

c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (See Box No. II).

3. ☐ **Unity of invention is lacking** (See Box No. III).

4. With regard to the **title,**

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

Salinosporamide derivatives as proteasome inhibitors

5. With regard to the **abstract,**

☐ the text is approved as submitted by the applicant.

☒ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings,**

a. the figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ as selected by this Authority, because the applicant failed to suggest a figure.

☐ as selected by this Authority, because this figure better characterizes the invention.

b. ☒ none of the figures is to be published with the abstract.

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Box No. IV Text of the Abstract (Continuation of item 5 of the first sheet)

Disclosed herein are 6-oxa-2-azabicyclo[3.2.0]heptane-3,7-dione or heterobicyclic γ-lactam-β-lactone derivatives of formula (I) that include a sulfonate ester, ester or ether group in the substituent at the 4-position as proteasome inhibitors. These Salinosporamide derivatives of formula (I) can be included in pharmaceutical compositions and can be used for treating or ameliorating a disease or condition such as cancer, a microbial disease or inflammation.